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United States. Its estimate of lung cancer mortality is nothing more than an exercise in mathematical modeling. Critics contend that the EPA analysis failed to properly include relevant uncertainties in its extrapolation exercise. If properly conducted, the estimates generated by the EPA's model would have included zero in its range of potential risk for non-smoker exposure to ETS.

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smokers to misrepresent themselves as non-smokers, and chose to adjust for it by using an unpublished scientific model that contains numerous inconsistencies, including assumptions based on non-representative data. The EPA report failed to address other sources of bias including respondent bias, generated by inaccurate recall of ETS exposure, and disease misclassification bias, arising from inaccurate diagnoses of lung cancer in the cases. The EPA report only considered possible confounders that were identified in the few studies on spousal smoking that actually addressed possible confounding agents. It ignored the large body of scientific literature that, independent of ETS exposures, identifies diet, personal medical history, genetics, lifestyle choices, occupational factors, and environmental factors as independent risk factors and potential confounders for lung cancer. Indeed, some of these potential confounders are of such magnitude that they are large enough to completely account for any reported association between spousal smoking and lung cancer.

The Review attempts to justify EPA's unorthodox lowering of the threshold for achieving statistical significance by stating: "Because a protective effect of ETS exposure on lung cancer risk seems biologically implausible, it is appropriate to use a one-side statistical test of the hypothesis of no effect at a 5% level of significance. Consistent with this criterion, the EPA calculated 90% confidence intervals rather than the more commonly used 95%

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confidence intervals." This does not, however, provide a justification for EPA's unprecedented rejection of the accepted two-tailed test for statistical significance, as employed in all but three of the 30 studies on spousal smoking. The issue here is not whether ETS is "protective," but whether or not it is associated with an increased risk of lung cancer. Only a two-tailed test can evaluate the latter. According to statisticians, the use of a one-tail test is only justified after a causal association has been proved.

By lowering the confidence interval from 95% to 90%, EPA doubled the possibility that a statistically significant association is simply a random or meaningless event. It's use of the lower 90% confidence interval contrasts with its use of the generally accepted 95% level in the 1990 draft of the ETS risk assessment and with its own routine use of studies employing the standard level in other carcinogen risk assessments. Many reviewers suggested that EPA's motivation for lowering the confidence interval from 95% to 90% was transparent because it was the only way it could claim a statistically significant association between marriage to a smoker and an increased risk of lung cancer. Interestingly enough, even after reanalyzing the studies using the lower confidence interval, EPA failed to obtain statistically significant overall associations from over two-thirds of the studies. Of the 11 U.S. studies, only one yielded a statistically

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significant overall association after reanalysis. All 11 of the U.S. spousal smoking studies considered by the EPA failed to report statistically significant results overall at the 95% confidence interval.

III. A CAUSAL ASSOCIATION?:

The Review applies a "number of criteria that have been developed to assess whether associations observed in epidemiologic studies are indeed causal." In its discussion of the causal criterion of "consistency," the Review suggests that "of the 31 epidemiological studies reviewed in the EPA report, 24 studies found an increased risk of lung cancer in never-smoking females exposed to spousal ETS. In nine of the 24 studies the risk increase was statistically significant." In actuality, 25 of the 31 studies on spousal smoking failed to report statistically significant overall associations for spousal smoking and lung cancer. Only six studies reported statistically significant increases for spousal smoking, and those studies failed to rule out possible biases and confounders as contributors to the reported associations. In addition, nine studies reported overall risks that were equivalent to 1.00 or less, suggesting a negative association between spousal smoking and non-smoker lung cancer. By any stretch of the imagination, these studies do not provide "consistency" of results.

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the "suspected carcinogens" reportedly identified in sidestream smoke and imputed to ETS have not been unequivocally proven as tumorigenic to any human tissue or, for that matter, to the lung tissue of laboratory animals.

The U.S. EPA's estimate that ETS causes 3,000 non-smoker lung cancer deaths per year in the U.S. is based upon the EPA's "reanalysis" of the epidemiologic studies on spousal smoking, 80% of which report statistically nonsignificant associations overall between spousal smoking and lung cancer in non-smokers. An average risk estimate from the spousal smoking studies was derived by the EPA and applied to the entire non-smoking population of the U.S. The estimate of lung cancer deaths was based upon projections and estimates from mathematical models and did not involve actual counts of lung cancer cases.

II. EPA META-ANALYSIS:

The Review correctly points out that "individual epidemiological studies of passive smoking and lung cancer could include only small numbers of subjects, leading to inconclusive results." Although more recent studies on spousal smoking contain an adequate number of cases to provide sufficient statistical power to detect possible effects, the EPA chose to combine instead select portions of the data from all available epidemiologic studies using

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is therefore misleading for the EPA to suggest that those kinds of data are amenable to a dose-response analysis.

For the criterion "biological plausibility," the Review reiterates the EPA's claim regarding the similarities between mainstream smoke and ETS. The implication is that a risk must therefore exist between exposure to ETS and lung cancer in non-smokers. Of course, this amounts to a simple analogy and does not provide a scientific evaluation of the data on ETS. "Biological plausibility" only suggests the compatibility of two hypotheses -- one for active smoking and one for ETS -- in relation to human disease. It is a conjecture incapable of either proving or disproving the case on ETS.

The public health community itself has recognized that the pervasive differences between mainstream smoke and ETS preclude any analysis of ETS using proxy data on mainstream smoke. Even the Surgeon General of the United States concluded in 1986 that knowledge of mainstream chemical composition is of limited assistance in evaluations of ETS. He wrote: "Comparison of the relative concentrations of various components of sidestream smoke and mainstream smoke provides limited insights concerning the toxicological potential of ETS in comparison with active smoking." (1986 Surgeon General's Report, 24)

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smoking exposure and without reference to actual exposure data on ETS constituents in the ambient air of workplaces, public places and other venues. More fundamentally, the problem with an upward adjustment for background exposure is that it represents circular reasoning on the part of the EPA. It presupposes that spousal smoking is indeed causally related to an increased risk of lung cancer among non-smoking wives, and that is precisely the issue to be proved by the EPA.

The studies analyzed by the EPA primarily address whether a woman's risk of lung cancer may be statistically associated with whether or not her spouse smokes. ETS "exposure" is defined in terms of "marriage to a smoker." The studies do not measure actual ETS exposure. Instead, they rely on questionnaire responses as to whether a woman's spouse smokes and how much -- a technique which relies completely upon an individual or surrogate's memory of ETS exposures throughout a lifetime. This, of course, is a notoriously inaccurate method for accurately assessing ETS exposure and there is certainly no way that such memories can accurately assess the amount of ETS exposure for a given individual.

Contrary to the claims of the Review, the EPA report did not assess all sources of bias or confounding in the individual spousal smoking studies. The EPA report recognized only one possible source of bias in its report, namely, the tendency of

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IV. RECENT STUDIES:

The Review notes that the EPA Report failed to consider two available studies on spousal smoking and lung cancer in the U.S. In one of those studies, involving 432 never-smokers, no overall risk was reported for spousal smoking. The second study, involving 210 never-smoking females, reported a statistically insignificant increased risk of lung cancer for spousal smoking. Given this, the Review nonetheless states that "if these studies had been included in the EPA analysis the results of both studies would most probably have supported the conclusion drawn by the EPA. . . ." In point of fact, had the data from those two studies been included in EPA's meta-analysis, the resulting pooled risk estimate for all U.S. studies would have failed to achieve statistical significance even at the EPA's relaxed level of evaluation, namely, the 90% confidence interval.

V. PUBLIC HEALTH IMPACT:

The EPA generated its estimate of lung cancer mortality for the United States on the basis of its meta-analysis of spousal smoking studies on U.S. females. Without regard to statistical significance or actual available data on male never-smokers or workplace exposures to ETS, the EPA extrapolated its estimate on spousal smoking to apply to all non-smokers in all venues in the

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The Review, in its discussion of the criterion "strength of association," correctly points out that all of the reported risks in the 31 spousal smoking studies are deemed "weak" by statisticians. All of the overall risk estimates are less than 2.55 and most are less than 1.5. These levels of reported risk could be accounted for by confounders or bias and are, at any rate, at the very detection limits for an epidemiologic study.

The Review states that "a statistically significant trend of increasing lung cancer risk with increasing exposure to ETS was found." The so-called statistically significant trends were derived by the EPA through still another "reanalysis" of the original data from the spousal smoking studies. None of the 31 epidemiologic studies relied upon by the EPA reported a statistically significant dose-response relationship. The EPA substituted a statistical test for trend for a true dose-response test. Unfortunately, as has been pointed out in comments from various statisticians, the EPA performed improper trend tests on the data, thus permitting them to draw conclusions regarding statistical significance. Moreover, the EPA's "reanalysis" of the data from the spousal smoking studies did not recognize the nonquantitative nature of the data. Actual exposure data were not employed in the spousal smoking studies. Instead, degrees of exposure depended upon estimates given by cases or relatives. It

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The EPA itself concedes (and thereby contradicts its own argument for biological plausibility) that there are substantial physical and chemical differences between mainstream smoke and ETS. For example, in Chapter 6, the EPA report states:

> This assumption [comparing MS and ETS to calculate lung cancer risks] may not be tenable, however, as MS and SS differ in the relative composition of carcinogens and other components identified in tobacco smoke and in their physico-chemical properties in general. . . .

Vast quantitative differences between ETS exposures and active smoking independently challenge the criterion of "biological plausibility." ETS constituents such as particulate matter and ambient nicotine have been measured in the ambient air. Based on those data, scientists have estimated that an individual's typical ETS exposure would be equivalent to the range of one to five cigarette equivalents per year. This exposure/dose estimate can be compared with an analysis presented in a recently published review in which scientists evaluated several epidemiologic studies on active smoking. They reported that smoking four to five cigarettes per day is not likely associated with a statistically significant increased risk of lung cancer. The same scientists estimated that the average individual exposed to ETS retains between 10,000 and 100,000 times less the smoke particulate matter of a active smoker.

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COMMENTARY:

"PASSIVE SMOKING AND LUNG CANCER: THE EPA REPORT"

Dutch Cancer Institute, Amsterdam

I. INTRODUCTION:

The recent classification of ETS as a "known human carcinogen" by the U.S. EPA was based on (i) an interpretation of epidemiologic studies on non-smoking wives of smokers and (ii) an extrapolation of selected data on active smoking to ETS. Consistent with the latter theme, the Review by the Netherlands Cancer Institute suggests that although sidestream smoke "has a composition different from the smoke inhaled by the active smoker," it nevertheless "contains similar carcinogenic and toxic agents . . ." and therefore, "it is not unlikely that inhalation of environmental tobacco smoke . . . is associated with an increased risk of lung cancer." However, the claim that mainstream smoke, sidestream smoke and ETS contain "similar carcinogenic and toxic agents" is an inference which ignores the vast physical and quantitative chemical differences among the three kinds of smoke. ETS is a highly dilute, dynamic mixture of sidestream smoke and exhaled mainstream smoke. Very few of the chemical constituents identified in mainstream or sidestream smoke have been identified in ETS in the ambient air. The general physical and chemical properties of the three kinds of smoke, including particle size and constituent-phase distribution, differ significantly. Moreover,

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a controversial technique known as meta-analysis. Meta-analysis can have utility when the studies that are combined are similarly designed and conducted and when similar data are compared with similar data. The epidemiologic studies on spousal smoking and lung cancer do not meet those criteria.

The Review misleadingly suggests that "information on exposure during childhood and at the workplace was available in only a few studies and, consequently, was not taken into account in the EPA analysis." In fact, sufficient workplace exposure data were reported in 11 of the 31 studies examined in the EPA risk assessment. Ten of the 11 studies reported no statistically significant increased risk for non-smoking females exposed to ETS at the workplace. Similarly, the EPA chose to ignore data on childhood exposures to ETS reported in 10 of the spousal smoking studies. Nine of the 10 studies reported results that were not statistically significant overall. Had meta-analyses been performed on the workplace and childhood exposure studies, the resulting combined estimates would indicate no increased risk.

The EPA "adjusted" the estimated risk generated by its meta-analysis of the spousal smoking studies "because of widespread exposure to ETS settings other than the home." Unfortunately, this upward "adjustment" of the risk estimate for spousal smoking was made without recourse to the epidemiologic data on workplace

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